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December 31, 2004

BY FEDERAL EXPRESS

Division of Dockets Management (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: **Docket No. 2004P-0070 CP1/CP2; FERRLECIT®**

We represent Watson Pharma, Inc., a subsidiary of Watson Pharmaceuticals, Inc. ("collectively Watson"), in connection with the above-referenced Citizen Petition.

Filed herewith in quadruplicate is Watson's reply to the enclosed numbered comments on the Petition submitted on November 21, 2004 by Teva Pharmaceuticals USA (copy attached).

1. Contrary to Teva's assertion, it is not incumbent upon Watson to show that all other processes besides Watson's manufacturing process will produce products inequivalent to FERRLECIT®. Rather, the burden is upon Teva or any other ANDA applicant to demonstrate that the active complex comprising its generic version of FERRLECIT® is "the same as" FERRLECIT®. 21 U.S.C. § 355(j)(2)(A)(ii)(I).

The active ingredient of FERRLECIT® is a highly complex macromolecule that is manufactured using a comprehensive process ensuring that the same active complex with the same physicochemical characteristics is consistently produced. (*See* Docket No. 2004P-0070/CP2, Aug. 17, 2004, at 1). The process is the product, since there is no identifiable active ingredient before creation of the FERRLECIT® final product. *Id.* at 2. Deviations from the manufacturing process can change the physicochemical characteristics of the active complex, which can adversely affect the safety of the active complex. *Id.* at 2. Accordingly, the same manufacturing process used by Watson must be utilized by generic manufacturers to assure that a generic company is producing the same active complex, or a

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substantially similar process under guidelines pre-established by FDA that will assure that the physicochemical properties of the active complex are not altered.*

2. The instant Petition's reference to iron dextrose products (*see* Docket No. 2004P-0070/CP1, Feb. 13, 2004, at 2-3) is of the utmost relevance, since FDA's experience with such products demonstrates that differences in molecular weight between generic and reference iron complexes can produce inequivalence in clinical safety and efficacy. *See Id.* at 7-8 (manufacturer of DexFerrum®, which had twice the molecular weight of reference product INFeD®, was required to conduct additional clinical studies to show that the products were therapeutically equivalent).

3(a) and 5. Teva's assertion that Watson "experienced failure at attempts to change aspects" of the manufacturing process for FERRLECIT® is misleading and inaccurate. As noted in the Citizen Petition, a temporary unknown change in the source of one of the ingredients in FERRLECIT®, and an investigation of a preservative-free version of the product, resulted in unexpected adverse events. The manufacturing process itself for the commercialized FERRLECIT® product has not changed for over 40 years. (*See* Docket No. 2004P-0070/CP1, Feb. 13, 2004, at 5).

3(b) and 3(c). Teva agrees with Watson that "physicochemical differences resulting from different methods of production could have a negative impact on the efficacy" of a generic version of FERRLECIT®, and that "not all processes will yield an equivalent safe and effective product." Thus, it is the responsibility of Teva and other generic applicants to use the same methods of production, or substantially similar methods of production under pre-announced FDA guidelines, to assure that this will not occur.

4 and 6. Watson's instant petition stresses that FDA should establish guidelines prescribing the manufacturing methods substantially similar to those used for FERRLECIT® to show that generic sodium ferric gluconate complex drug products will contain the same active complex as FERRELCIT®, before any

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* The decision in *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998) which Teva cites actually supports Watson's position, because there the court affirmed FDA's requirements that generic follicle-stimulating hormone drug products have the same primary structure (protein backbone with a specific amino acid sequence as Pergonal®, **and** that the manufacturing process for generic products control batch-to-batch uniformity by using the same USP rat potency tests as used by Pergonal®'s manufacturer. *Serono,* 158 F.3d at 1320.

ANDA is received for substantive review. (*See* Docket No. 2004P-0070/CP2, Aug. 17, 2004, at 2). This is a reasonable, scientifically sound approach, not an attempt to prevent FDA's review of ANDAs that contain data meeting such guidelines.

For example, Wyeth-Ayerst filed a citizen petition in 1995, urging FDA not to receive for substantive review or approve any ANDA for a generic synthetic conjugated estrogen drug product, until adequate data were generated to characterize the individual active estrogen ingredients in the innovative drug product Premarin® to assure that the active estrogen ingredients in a given generic product would be the same as the active estrogen ingredients in Premarin®. FDA concurred with Wyeth-Ayerst in a 1997, subsequently issued a guidance document in 2000 establishing a method for qualitative chemical characterization and pharmaceutical equivalence of individual estrogen ingredients, but has not to date approved any ANDA for a generic version of Premarin®.

For the reasons set forth in the Citizen Petition and herein, it is respectfully submitted that the Petition be granted in all respects.

Sincerely yours,

Charles J. Raubicheck

CJR:bav
Encl.

cc: Watson Pharma, Inc.